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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/846,933	04/30/97	CLELAND J	P0825BC3

EXAMINER

HM12/0317

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ART UNIT	PAPER NUMBER
1641	13

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12/22/98 and 2/22/99

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 4-9, 23-27 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1, 4-9, 23-27 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☒ Interview Summary, PTO-413 (Paper #10)
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

DETAILED ACTION

The Group and/or Art Unit location of your application in the Patent and Trademark Office may have changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1641.

The text of those sections of U.S. Code not included in this Office Action can be found in a prior Office Action.

The Examiner acknowledges receipt of the amendment filed February 22, 1999.

Continued Prosecution Application

The request filed on December 22, 1998 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/846,933 is acceptable and a CPA has been established. An action on the CPA follows.

In this application:

Claims 1, 6, and 23-27 were amended.

Claims 1, 4-9, and 23-27 are now pending and under examination.

Response to Amendment

Applicant's arguments filed February 22, 1999 have been fully and carefully considered and they are not deemed to be persuasive regarding those rejections which are maintained.

(1) The objections to the drawing are maintained for reasons of record.

(2) The objection to claim 7 for failing to comply with 37 CFR 1.75(b) is withdrawn.

(3) The rejection of claims 1, 4-9, and 23-27 under 35 U.S.C. 112, first paragraph is maintained.

Applicant asserts that the specification provides support for the term "beginning at the completion" of the phases at page 5, lines 30-32; page 6, lines 10-14; and Figure 8. However, these locations do not suggest the phases "beginning at the completion" of the previous phase. Furthermore, although Figure 8 depicts the %release, there is no clear indication where the phases begin and end as recited in the claims.

(4) The rejection of claim 1, 4-9, and 23-27 under 35 U.S.C. 112

(4) The rejection of claim 1, 4, 9, and 23-27 under 35 U.S.C. 112, second paragraph is withdrawn.

(5) The rejection of claims 1, 4, 9, and 23-27 under 35 U.S.C. 103 as being unpatentable by Eppstein et al is withdrawn.

(6) The rejection of claims 1, 4, 9, and 23-27 under 35 U.S.C. 103 as being unpatentable by Sanders et al in view of Eldridge et al (Mol Immun) and further in view of Jeffery et al is maintained.

Applicant asserts that Sanders et al do not provide credible data regarding release rates, and therefore, do not teach or suggest triphasic release. Applicant also asserts that Jeffery et al is not directed to a triphasic release system and Eldridge et al teach multiphasic release, but do not teach the method of the claimed invention.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Sanders specifically teach a triphasic release profile. In addition, Sanders et al teach that the model used "provides a reliable indication of the duration of compound release, although not of the release rate". (Page 1296, first column). Furthermore, Sanders et al disclose that a 69:31 copolymer of relatively high intrinsic viscosity gives a clearly triphasic

compound release over 90 d. (Page 1296, second column). Moreover, Sanders et al teach that several factors, such as parameters of the copolymer, the molecular weight and polymer composition, and intrinsic viscosity affect the release profile and rate of release. It is also noted that the claims do not recite the release rate or "non-blended".

Although Jeffery et al do not specifically teach the triphasic release pattern, the reference is cited to show the incorporation of antigens in poly(lactide-co-glycolide) systems. Similarly, Eldridge et al teach the encapsulation of antigen. Furthermore, Eldridge et al teach that discrete release of antigens can be achieved by varying parameters such as copolymer ratio and size.

(7) The rejection of claims 5-7 under 35 U.S.C. 103 as being unpatentable by Sanders et al, Eldridge et al, and Jeffery et al (as applied to claims 1, 4, 9, and 23-27), and further in view of Wang et al is maintained.

Applicant asserts that Wang et al teach away from the claimed invention and provides no motivation to design microspheres that release antigen in distinct initial burst, followed by a phase of relatively low release.

Although Wang et al is not directed to triphasic release pattern, the reference demonstrates that it is known in the art of vaccination to combine adjuvants with antigens. Similarly, it is also known to combine the two elements for release from microspheres.

(8) The rejection of claim 8 under 35 U.S.C. 103 as being unpatentable by Sanders et al, Eldridge et al, and Jeffery et al (as applied to claims 1, 4, 9, and 23-27), and further in view of Newman et al is maintained for reasons of record.

The following are new grounds of rejections:

Specification

Claim 1 is objected to because of the following informalities:

Claim 1, lines 7-8, where "from from" should be --from--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1, 4-9, and 23-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention.

Claim 1 was amended to recite "1 milliliter of aqueous antigen per 3 gram of polymer or less". However, the specification as originally filed does not provide support for the limitation of "or less".

Claim 1 recites the antigen is released from the microspheres over a period of "about 1 to 2 days". However, the specification as originally filed does not provide support for this limitation.

Claims 1, 4-9, and 23-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "1 milliliter of aqueous antigen per 3 gram of polymer or less". It is not clear what Applicant intends as there is no lower limit. Therefore, the metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 9, and 23-27 are rejected under 35 U.S.C. 103 as being unpatentable by Floy et al.

Floy et al ("Design of Biodegradable Polymer Systems for Controlled Release of Bioactive Agents". In: Polymeric Delivery Systems: Properties and Applications. MA El-Nokaly et al (eds). American Chemical Society, Washington DC, 1993) teach a biodegradable system comprised of poly (D,L-lactide-co-glycolide)(PLGA) for delivery of peptides, proteins, and drugs. (See especially Abstract; and page 156)

Floy et al teach drug release profiles from these microspheres typically exhibit a triphasic release pattern. This

pattern is characterized by an initial, rapid release of the encapsulated compound during the first few days. A latent period then occurs where little of the compound is released. The latent period is then followed by a major phase of drug release. (See especially page 156, last two paragraphs).

Moreover, Floy et al teach that copolymer ratio, device geometry, molecular weight and intrinsic viscosity can affect the biodegradation and release profile of the polymer. (See especially pages 156 and 157)

Although Floy et al do not teach the specific ranges recited in the claims, the reference teaches that the parameters can be varied for optimization of the delivery system.

Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. See In re Aller, 220 F.2d 454, 105 USPQ 322,325 (CCPA 1955).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to encapsulate antigens within microspheres of various diameters, compositions, and viscosity in order to deliver the antigen for release in various amounts and at various duration, absent evidence to the contrary or unexpected results.

Claims 5-7 are rejected under 35 U.S.C. 103 as being unpatentable by Floy et al (as applied to claims 1, 4, 9, and 23-27) in view of Immunization Practices Advisory Committee.

The teachings of Floy et al were set forth above. The reference, however, differs in not teaching an adjuvant with the antigen.

Immunization Practices Advisory Committee (Clinical Pharmacy 8:839-851, 1989) teach that adjuvants can be administered with antigens in order to enhance an immune response. (See especially page 840)

Given the teachings of the prior art that adjuvants can be combined with antigens in order to enhance an immune response, it would have been obvious to one of ordinary skill in the art at the time the invention was made to similarly combine the two elements in a microsphere, absent evidence to the contrary or unexpected results.

Claim 8 is rejected under 35 U.S.C. 103 as being unpatentable by Floy et al in view of Immunization Practices Advisory Committee and further in view of Newman et al.

The teachings of Floy et al and Immunization Practices Advisory Committee were set forth above. The references teach

the expected benefit of combining an adjuvant with an antigen. The references, however, differ in not teaching the use of QS21 as the adjuvant.

Newman et al (AIDS Research and Human Retroviruses 8(8):1413-1418, 1992) teach that QS21 has the advantages of augmenting antibody responses. (See especially pages 146, column 2; and page 1417, paragraph 1)

Given the teachings of the prior art that QS21 is non-toxic and augments antibody responses, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include QS21 as an adjuvant in the vaccine composition taught by the above references since QS21 can be used as a safe adjuvant in vaccine compositions for establishing immunological memory.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to V. Ryan whose telephone number is (703)305-6558.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Papers related to this application may be submitted to the Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax number for Art Unit 1641 is (703)308-4242.

V. Ryan
Patent Examiner/Art Unit 1641
March 1999
Ryan/vr

James C. Housel
JAMES C. HOUSEL 3/15/99
SUPERVISORY PATENT EXAMINER